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The AGEs inhibitor pyridoxamine prevents kidney injury and dysfunction in mice fed high-fat high-fructose diet.

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Background and aims: Recent evidence suggests a key role of the local accumulation of diet-derived Advanced Glycation End-Products (AGEs) in evoking kidney injury/dysfunction associated with chronic exposure to hypercaloric diets. Pyridoxamine, a structural analog of vitamin B6 that exerts anti-glycative effect by interfering with oxidative macromolecular damage, is now in phase 3 clinical efficacy trial to delay chronic kidney diseases progression in patients with type 1 diabetes. However, so far, the potential beneficial renoprotective effects of pyridoxamine in type 2 diabetes and obesity have not yet been investigated. Thus, we aimed to study the role of dietary supplementation of pyridoxamine as preventive strategy to counteract the deleterious renal effects evoked by hypercaloric diet in mice.

Materials and methods: C57Bl/6J mice were fed a standard diet (SD, n = 16) or a diet enriched in fat (40%) and fructose (45%) (HFHF, n=16) for 12 weeks. At week 3, two subgroups of SD and HFHF mice started to receive pyridoxamine supplementation (150 mg/kg/day) in the drinking water. At week 12, mice were sacrificed and urine, plasma and kidneys were collected for Western blot, ELISA, histological and immunohistochemical analysis.

Results: When compared to SD mice, HFHF fed mice showed increased body weight ($25,2 \pm 1,1$ vs. $33,7 \pm 2,1$ g, $p < 0,001$) and impaired glucose homeostasis (fasting glycaemia $72,80 \pm 18,89$ vs. $138,80 \pm 12,68$ mg/dL, $p < 0,001$). Pyridoxamine administration significantly improved fasting glycaemia ($104,60 \pm 9,71$ mg/dL, $p < 0,05$) but not body weight ($34,7 \pm 3,5$ g).

Renal function was strongly impaired by hyper-caloric supplement (serum creatinine 0.70 ± 0.06 vs 1.13 ± 0.15 mg/dL $p < 0.05$; urine albumin 74.44 ± 14.18 vs 265.07 ± 15.43 μ g/mL, $p < 0.001$) and, most notably, pyridoxamine significantly prevented the renal function derangements (serum creatinine 0.66 ± 0.03 , $p < 0.05$ vs HFHF; urine albumin 195.28 ± 34.68 μ g/mL, $p < 0.05$ vs HFHF). Kidney morphology of HFHF fed mice presented strong vacuolar degeneration and loss of tubule brush border, both clearly attenuated by pyridoxamine administration. The HFHF-induced morphological and functional derangements were associated with a robust increase in the local expression of AGEs receptor (RAGE) and pro-fibrogenic markers (fibronectin, vimentin, SMAD2/3) as well as a significant activation of the pro-inflammatory NF- κ B and Rho/ROCK signaling pathways. Interestingly, pyridoxamine prevented the diet-induced overexpression of RAGE and pro-fibrogenic markers as well as the activation of the inflammatory signaling cascades.

Conclusion: The present study demonstrated for the first time that the administration of the anti-glycative compound pyridoxamine reduced diet-dependent kidney injury and dysfunction by interfering with local AGEs accumulation, thus resulting in reduced activation of the pro-fibrotic and inflammatory cascades.